UiT The Arctic University of Norway

Faculty or Health Sciences, Department of Community Medicine

Hepatitis C virus screening attendance and its relation to age, education, geographic region and perinatal mortality - Georgian Birth Registry 2017/2018

Aleksandra Pajovic

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Supervisor: Erik Eik Anda

Co-supervisor: Therese Haugdahl Nøst

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Aleksandra Tromsø, May 2020

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Abstract

Introduction: Hepatitis C virus (HCV) causes a liver disease hepatitis C, which can manifest in acute and chronic form, with potentially life-threatening complications. Globally, in 2017, there were approximately 115 million HCV infected people. Currently, screening for HCV during pregnancy is offered to all pregnant women in a very few countries in the world. Importance of screening every pregnant woman is based on the fact that many HCV infected pregnant women are undetected when screening is risk based. It was estimated that the risk of vertical transmission of HCV (from mother to child) is 5.8%. Infants born to HCV infected mothers have poor birth outcomes such as low birth weight (LBW) and intrauterine foetal growth restriction (IUGR), which are main causes of overall perinatal mortality (PM). In Georgia, country located at the border between Europe and Asia, hepatitis C is burning public health problem, with prevalence of 7.7% in 2015. Screening for HCV is from 2015, offered to all pregnant women through the Maternal and Child Care program. In 2017/18, Georgia had PM of 12.9 per 1000 births.

Purpose: The purpose of this thesis was to compare HCV screening attendance of pregnant women in Georgia, according to age, education, region of antenatal care (ANC) clinic at the firs ANC visit, and PM.

Material and methods: Data were extracted from the Georgian Birth Registry (GBR). All women who gave birth in 2017/18 were included in the study and categorized into screened and non-screened groups, while non-screened group was further divided into two groups, with and without ANC visits. After exclusions, the study sample included 103 079 women. The

descriptive statistics were presented by using percentages, means and standard deviations and the differences were tested by Chi-square test and one-way ANOVA. Binary logistic regression analysis was used to estimate multivariable adjusted odds ratios (OR) with 95% confidence intervals (CI), for being screened according to age, education, and region of ANC clinic, as well as to estimate the association between PM and HCV screening attendance adjusted for age, birthweight of a new born, and complications at delivery.

Results: The odds of being screened was 9% lower for women older than 34 compared to the women in the age-group 25-34 (95% CI 0.85-0.97). Women with only primary education had 49% lower odds of being screened compared to women with secondary education (95% CI 0.47-0.55). Women from other regions in which a woman had ANC visit had significantly lower odds of being screened compared to Guria region, the region with lowest proportion of non-screened women. Noticeable differences in screening attendance were also observed between ANC clinics in Tbilisi. There was no association between HCV screening attendance overall and PM in the multivariable binary regression analysis (OR=0.98, 95% CI 0.79-1.22).

Conclusion: Differences in age and education were observed between screened and non-screened pregnant women. There were considerably differences in screening attendance rates between regions in Georgia, as well as between ANC clinics in Tbilisi. There was no association between HCV screening attendance and PM.

Abbreviations

HCV	Hepatitis C Virus
RNA	Ribonucleic Acid
HBV	Hepatitis B Virus
LC	Liver cirrhosis
HCC	Hepatocellular carcinoma
IgG	Immunoglobulin G
IgM	Immunoglobulin M
PWID	People who inject drugs
PM	Perinatal mortality
LBW	Low birth weight
IUGR	Intrauterine foetal growth restriction
ENDs	Early neonatal deaths
ANC	Antenatal care
GBR	Georgian Birth Registry
ICD	International Classification of Diseases
OR	Odds Ratio
CI	Confidence Interval
SES	Socioeconomic status

1 Introduction

1.1 Hepatitis C Virus

Hepatitis C Virus (HCV) is a virus in the family of RNA viruses called the Flaviviridae (1). This virus can cause the liver disease Hepatitis C, which is a major health concern worldwide. Acute hepatitis C develops within one to three months after infection and it is defined as presence of clinical symptoms and/or signs of hepatitis C for a period of 6 month after initial infection (2). Symptoms include nausea, vomiting, weakness, muscle pain, and fever (3). However, the acute form of hepatitis C may go unnoticed due to absence of- or mild symptoms. Usually, patients without strong clinical indication will not be tested for HCV which make them under high risk for spreading this infection (2). It is estimated that between 15%-40% of people with acute hepatitis C can clear the virus spontaneously, without treatment. Spontaneous clearance is more likely to happen within the first 12 months from initial infection. A meta-analysis has shown that young female patients with symptoms of acute hepatitis C, co-infected with hepatitis B virus (HBV), and those who have a certain genotype, the HCV genotype 1, have increased possibility for spontaneous HCV clearance (4).

Without treatment, between 50% and 80% of patients with acute hepatitis C infection develop the chronic form of the disease (5). Chronic hepatitis C is defined as persistence of virus in the blood more than 6 months after presumed initial infection (2), and this disease is associated with high risk of life-threatening complications. Described symptoms of acute hepatitis C can be present in chronic for as well, while the presence of dark yellow urine, yellow colouring of the skin and eyes, and bleeding or bruising tendencies are signs of liver

damage, and more specific signs of chronic hepatitis C (3). Liver cirrhosis (LC) and hepatocellular carcinoma (HCC) are the stages of advanced HCV-related liver diseases (6). Not all HCV infected patients develop LC and HCV-related HCC. The prevalence of LC in chronic hepatitis C patients is around 20% and the incidence of HCV-related HCC is 4%-5% per year in patients with LC (5, 7, 8). Liver tissue damage caused by HCV can be repaired by the liver and replaced by scar tissue. Thus, the liver's ability to function normally is reduced (9). Studies have also shown that HCV infection is associated with higher risk for insulin resistance, Diabetes Mellitus type 2, and kidney diseases (5).

An estimated 170 million people worldwide are currently infected with HCV of whom 99 million are acute infections and 71 million chronic infections (10). It is difficult to determine whether a person has an acute or chronic form of hepatitis since the symptoms presented in these two forms of the disease can be rather similar. On the other hand, unlike chronic form, acute hepatitis C can be asymptomatic. Detection of anti-HCV Immunoglobulin G (IgG) antibodies, HCV ribonucleic acid (RNA) in serum or plasma, as well as increased levels of alanine aminotransferase are all good indicators of acute hepatitis, but can also be observed in patients with the chronic form. With progress of infection, the concentration of IgG antibodies increases, hence the anti-HCV IgG antibody level is the most reliable indicator to differentiate between acute and chronic hepatitis (11).

1.2 Epidemiologic profile of HCV in Georgia

The global HCV antibody-positive population was estimated at approximately 115 million people in 2017 and of those 10% resided in Eastern Europe and Central Asia (11.3 million) (12, 13).

Georgia is a country located between Eastern Europe and Western Asia, bordered by Azerbaijan, Armenia, Turkey, Russia and the Black Sea, with an estimated population of 3.99 million in 2020. Until 1991, Georgia was part of the Soviet Union, when it declared independency. Georgia is divided into two autonomous republics, nine regions, and one city. The largest city is the capital Tbilisi, with a population of 1.5 million (14). Georgia's health system has undergone major reforms over the last 20 years. From 2007 to 2012 government provided health insurance packages with certain health services for households below the poverty line. Private insurance companies were mediators between government and health care users (15). In order to improve the quality of health care and improve access to health care for every citizen, the State Universal Health Care Program was launched in 2013, with a minimum package of services offered to citizens who cannot afford private insurance. Currently, a large number of contract employees receive a specific package of health services covered by the employer, while from 2017 private health insurance is the only option for households with high income (15).

In Georgia, high prevalence of hepatitis C is a severe public health problem. In 2017, there were 7860 new cases of hepatitis C recorded. The estimated anti-HCV (HCV antibody-positive) prevalence of the disease in 2015 was 7.7%, whereas 5.4% of the population had active disease (16). The highest prevalence of chronic hepatitis C in 2015 was among men in age-group 30-49 (15.7%), while the prevalence among women in the same age group was

lower (2.2%). The reasons for high transmission of hepatitis C virus was extensive drug trafficking and increased number of people who inject drugs (PWID), as likely consequences of civil war in the period 1991-1993 (17). By November 2019, 55.9% of the male population and 57.9% of the female population have been screened for HCV, and the highest percentage of screened was in the 30-59 years age group (18). World`s first national hepatitis C elimination program was launched in Georgia in April 2015, supported with technical assistance by the U.S. Centre for Disease Control and Prevention, and treatment donated by pharmaceutical company Gilead Sciences. The goal of HCV elimination program was to reduce prevalence of chronic hepatitis C by 90% until 2020 by diagnosing 90% of people living with HCV, to treat 95% of those diagnosed, and to cure 95% of those treated. The strategy of the elimination program includes improvements in prevention, diagnostics and treatment. Screening was conducted among vulnerable groups such as PWID, men who have sex with men, sex workers, HIV/AIDS patients, tuberculosis patients, and patients on haemodialysis (17). The treatment program utilize a new antiviral drug Sofosbuvir provided by Gilead Sciences. Tsertsvadze *et al.* reported that in period April 2015 - March 2018, 35.1% of people living with HCV were diagnosed, 30.2% started treatment with direct-acting antiviral medications and 19.4% achieved sustained virological response (19). Up to February 2019, prevalence of adult chronic hepatitis C was reduced by a median 37%, incidence of chronic hepatitis C by 37%, and chronic hepatitis C mortality by 14%. The achieved results show improvement in the disease control even though Walker *et al.* suggested that the goals of the program are unlikely to be achieved by 2020 (17).

1.3 HCV in pregnancy

Hepatitis C in pregnancy carries risks for both mother and child. Adverse maternal outcomes include higher risk of development of intrahepatic cholestasis of pregnancy, premature ovarian senescence, gestational diabetes, and preterm delivery. Pregnant women with HCV have higher rates of miscarriages compared to HBV infected women (20). The association between gestational diabetes in HCV-infected women was found only in women who had obesity during pregnancy (21).

Vertical transmission of HCV, i.e. from mother to child, is possible during all three trimesters of pregnancy, delivery or the neonatal period, and is the leading cause of HCV infection in children (20, 21). It is estimated that approximately 60% of children under 19 years of age with HCV have acquired the infection through vertical transmission (22). In most cases, the transmission of the virus was found to be in peripartum (shortly before, during, and immediately after giving birth) or in the late intrauterine period (23). On the other hand, elective caesarean section before membrane rupture as a form of delivery was found to have a lower transmission risk compared to vaginal or emergency caesarean-section delivery (24, 25), although some studies suggest that there is no clear benefit from caesarean-section on viral transmission (26).

Even though antiviral treatment is not recommended during pregnancy (27), it is speculated that treatment to decrease viremia (the presence of virus in the blood) in pregnant women infected with HCV could reduce the risk of vertical transmission (28). A meta-analysis showed that the risk of vertical transmission for infants from untreated HCV-positive mothers was 5.8% (21). Kushner and Terrault showed that there was no risk for vertical transmission in HCV antibody positive mothers without detectable HCV RNA, i.e. that were successfully

treated before pregnancy or have spontaneously cleared the virus (23). Another study suggests that there is still risk of vertical transmission for such mothers, but that it is lower compared to HCV RNA-positive mothers (29).

There is convincing evidence that infants born to women infected with HCV are more likely to have poor birth outcomes as preterm birth, low birth weight, intrauterine foetal growth restriction (IUGR), and congenital anomalies (30, 31). However, it was suggested that poor pregnancy outcomes, as well as poor birth outcomes may be a consequence of confounding factors, such as smoking, alcohol use, intravenous drug use, poor prenatal care and other ongoing or past risk behaviours (23).

Safir *et al.* reported higher perinatal mortality (PM) in new borns of HBV or HCV infected mothers compared to uninfected mothers (2.3% and 1.3%, respectively) (32). Strong associations were noticed between HCV infection and LBW as well as IUGR, which were leading causes and significant contributors to overall perinatal morbidity and mortality (33). PM is defined as sum of stillbirths and early neonatal deaths (ENDs) (34). In Georgian national guidelines, stillbirth is defined as birth of foetus without any sign of life at 22 complete gestational weeks or more, or, when gestational age is unknown, birthweight of more than 500 grams. ENDs are defined as deaths within first seven completed days of life (35). In 2017/18, Georgia had PM of 12.9 per 1000 births (36). Leading cause of death for stillbirths were maternal conditions, even though for 80% of stillbirths cause of deaths were unknown. The majority of ENDs had preterm delivery (58%) and congenital malformations (23%) reported as the cause of death (37). Manjavidze *et al.* showed that women without any ANC visit during pregnancy had two time higher odds for PM compared to pregnant women who had ANC visits during pregnancy (36).

1.4 HCV screening

The American College of Obstetricians and Gynaecologists and the Centre for Disease Control and Prevention recommend risk-based screening for HCV in pregnant women who are under risk (20), which is the policy adopted by most countries. The risk factors for the general population are injection drug use, use of illicit intranasal drugs, receipt of blood transfusions or organ transplants before 1992, receipt of certain blood products prior to 1987, receipt of blood products from an HCV-positive donor, treatment with long-term dialysis, percutaneous or parenteral exposure in unregulated settings, history of incarceration, risk of HIV, and history of chronic liver disease of unknown ethology (20, 38). However, there is an opposition to risk-based approach, since it has been estimated that many HCV positive pregnant women without any risk factor for HCV infection remain undetected during their pregnancies (39). General screening of pregnant women would ensure that all infected women are detected and children born to HCV-infected mothers are identified, tested and, if needed, treated (39, 40). Georgia introduced universal screening for all pregnant women in December 2015, implemented into the Maternal and Child Care program (41).

Screening for hepatitis C is performed by testing a blood sample. There are two methods used in screening, an indirect and a direct test (5). With the indirect test, antibodies induced by viral infection are detected. Two types of antibodies include IgM for recent infection (acute form) and IgG for recent or past infection (chronic form), although anti-HCV IgM could be also detected in 50%-70% of chronic hepatitis C patients. A direct test includes virus isolation and/or detection of viral particles such as antigens and viral RNA. The direct test is conducted if an indirect test for anti-HCV antibodies is positive (5).

Universal health coverage for pregnant women in Georgia includes maternal care, and covers antenatal care visits. Antenatal visits are funded by the government, and are offered eight times, which ensures monitoring of foetus and pregnant woman. Screening for HCV, along with HIV, syphilis and hepatitis B is offered to all pregnant women, free of charge and is performed at clinics for antenatal care (ANC) (42). Screening for HCV is usually performed around week 11th-13th of pregnancy, although it can be performed at any time during pregnancy.

1.5 Georgian Birth Registry

The Georgian Birth Registry (GBR) is a digital medical birth registry with national coverage, and was initiated on 1st of January 2016. Reporting to the registry is mandatory for all health care facilities in Georgia that provide antenatal, birthing or post-natal care to provide information. Doctors or other trained medical personnel are responsible for collecting information. The clinics or hospitals are reimbursed when the information provided to the Registry is complete (43).

Currently more than 400 variables are recorded in GBR (44) which include medical and pregnancy history of the mother, maternal and paternal characteristics, information regarding the current pregnancy, the delivery, and on the new born. Information about hepatitis C screening attendance is also available in the GBR (43).

From 2017, all medical facilities that provide birthing and post-natal care are required to notify the Ministry of Health, the GBR, and the National Centre for Disease Control and Public Health (NCDC) of all stillbirths and neonatal deaths within 24 hours (37).

1.6 Public health context of the thesis

Even though there are no effective antiviral drugs that would decrease the risk of vertical transmission of HCV, identification of all pregnant women that are HCV positive is important. It would allow adequate treatment for both mother and the child, follow up of HCV infected women, decrease the possibility for mother to child transmission in future pregnancies, and finally protect medical professionals included in medical assistance during childbirth. The HCV prevalence in general population in Georgia, according the last survey conducted in 2015 was 7.7% (16). In order to achieve given the goals that are set by the HCV elimination program, it is necessary for all the pregnant women to be screened for HCV in order to capture all cases.

The aim of this thesis was to identify demographic differences between pregnant women in Georgia that were screened for HCV and those that were not, to assess differences in hepatitis C screening attendance during pregnancy between regions in Georgia, as well as between ANC clinics in Tbilisi, and to determine if there is a difference in PM according to HCV screening attendance. A cross-sectional study design was used and data from the GBR.

1.7 Research questions

1) Can selected sociodemographic factors help explain why some pregnant women in Georgia do not undergo recommended screening for HCV?

2) Are there differences in HCV screening attendance between regions in Georgia?

3) Are there differences in HCV screening attendance between ANC clinics in Tbilisi?

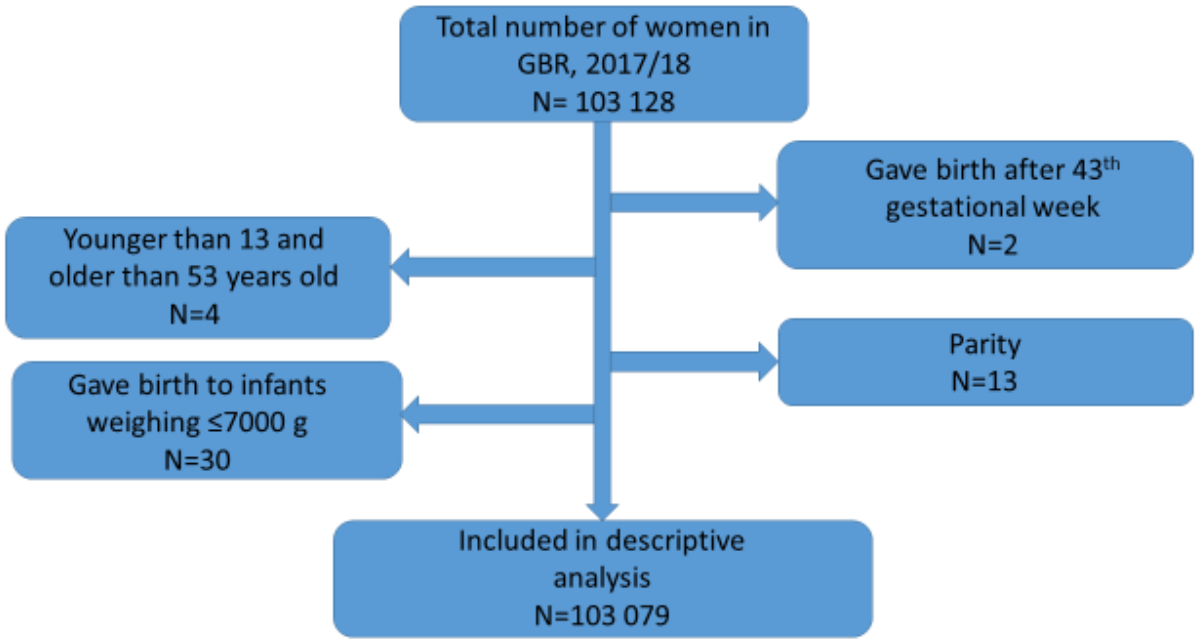
4) Is there a difference in PM according to HCV screening attendance?

2 Material and methods

2.1 Study sample

The initial sample consisted of 103 128 women. Several biologically implausible outliers were removed from the final study sample; women younger than 13 and older than 53 years (N=4), those who gave birth to children weighing 7000 grams or more (N=30), and those with more than 15 deliveries after 22th gestational week (parity) (N=13). In addition, women who gave birth to infants after 43th gestational week were also excluded (N=2). Hence, the analytical study sample used in the descriptive analysis consisted of 103 079 women (Figure 1) .

Figure 1. Exclusion criteria and number of women excluded in the study sample



2.2. Information on HCV screening attendance

The non-screened group consisted of women both with and without any ANC visits. In order to properly capture differences between screened and non-screened group, the non-screened group was further divided into those with and without ANC visits. Therefore, for the purpose of descriptive analysis, the independent "screening Hepatitis C" variable was categorised into: screened group, non-screened group with ANC visits, and non-screened group without ANC visit. In the regression analysis, the screening variable was dichotomized into two categories – screened and non-screened.

2.3 Information on age, level of education, and region of ANC clinics at the first visit

The "age" variable was divided into three groups: ≤24, 25-34, ≥35. In multivariable binary regression analyses, age group 25-34 was used as the reference group.

The "education" variable was categorized based on the last completed level of education: primary, secondary, bachelor and postgraduate. In the GBR, education is divided into nine groups, which were collapsed into three categories: primary = preschool, incomplete secondary school; secondary = complete secondary and technical/professional education; bachelor and postgraduate = bachelor degree, higher and postgraduate. Secondary education was used as the reference group in the multivariable logistic regression analyses.

The GBR contains information about the region of ANC clinic in which a woman had the first antenatal visit. In the GBR, the "region" variable was divided into eleven groups, based on geographic regions in Georgia: Guria, Adjara, Imereti, Kakheti, Kvemo Kartli, Mtskheta-

Mtianeti, Racha-Lechkhumi and Qvemo Svaneti, Smagrelo and Zemo Svaneti, Samtskhe-Javakheti, Shida Kartli, and Tbilisi. For the purpose of this thesis, autonomous republic and city were defined as regions. Guria region (Figure 3) was chosen as the reference group in multivariable logistic regression analysis as region with smallest proportion of non-screened women.

2.4 Information on ANC clinics in Tbilisi

Variable "ANC clinics in Tbilisi" included information on the number of screened and non-screened women in all of 263, public and private, ANC clinics in Tbilisi. Ten ANC clinics in Tbilisi that were included in the analysis were those with the highest registered number of non-screened women. The use of names of ANC clinics is not permitted thus the clinics were labelled with numbers 1-10.

2.5 Information on perinatal mortality

In the GBR, variable "perinatal mortality" includes both stillbirths and ENDs. Stillbirth is defined as birth of foetus without any sign of life at 22 complete gestational weeks or more, or, when gestational age is unknown, birthweight of more than 500 grams. ENDs are defined as deaths within first seven completed days of life. For the purpose of analyses here, variable "perinatal mortality" was created as a binary, Yes/No.

2.6 Covariates

Variables “birth weight” and “complications during delivery” were used as adjustment factors in the analysis of screening attendance and perinatal mortality (37, 45).

Complications have been registered with an International Classification of Diseases code (ICD; 10th revision). In 2017 and 2018, complications during delivery were reported for 13 348 (12.9%) childbirths. The number of different diagnoses based on ICD10 codes was around 50, with few deliveries per diagnosis. Hence, the variable “complication during delivery” was merged from the data from 2017 and 2018, and made as binary (Yes/No).

Variable “parity” included information on how many times a woman had given birth after 22th gestational week or, if gestational age was unknown, had given birth to an infant of at least 500 grams, including the current delivery. Variable “parity“ was made as categorical, with three categories: 1 = 0 or 1 delivery; 2 = 2-4 deliveries; 3 = 5-15 deliveries.

2.7 Statistical analysis

Characteristics of included women are presented using percentages, means and standard deviations, and analysed with Chi-square test for categorical variables, and one-way ANOVA for continuous variables. Binary logistic regression analysis was used to estimate multivariable adjusted odds ratios (OR) for being screened according to age, education, and ANC clinic region with 95% confidence intervals (CI). For this part of the analysis, women who had missing information on region of ANC clinic, i.e. who did not have antenatal visits during pregnancy (N=5786) in 2017 and 2018, and women with `unknown` educational status (N=8381) were excluded. Number of women included in binary logistic regression was

88 912. Sensitivity analysis was performed by also including parity into multivariable logistic regression model. Binary logistic regression was also used to estimate the association between PM and HCV screening attendance adjusted for age, birthweight of a new born, and complications at delivery. For this part of the analysis, non-screened women consisted of both those with and without ANC visits (N=103 079). A sensitivity analysis was performed in which education, regions and parity were also included in the multivariable logistic regression model. Another sensitivity analysis was performed to compare PM between screened women and non-screened women without any ANC visits only.

All analyses were performed using IBM Statistics Package for Social Sciences (SPSS) for Windows, Version 26.0. Armonk, NY: IBM Corp.

2.8 Ethics

The University of Tromsø - the Arctic University of Norway has permission to use data from the GBR for scientific purposes. Regional Committee for Medical and Health Research Ethics of Northern Norway has approved the use of data (2017/404/REK Nord).

The dataset exported from Georgia and used for analyses was anonymous.

3 Results

3.1 HCV screening attendance

In 2017 and 2018, number of women who had not been screened for HCV in pregnancy was 14 735 (14.3%), of whom 8949 had at least one ANC visit, whereas 5786 women had no antenatal visits registered in the GBR (Table 1).

3.2 Differences in age and education according to screening attendance

Mean age of screened, non-screened women with, and without ANC visits was 28.11, 28.25 and 28.42, respectively. The proportion of women in the age-group ≥35 years of age was highest in the non-screened group without any visit, 18.2%, compared to 16.0% in non-screened group with ANC visits, and 14.8% in the screened group (Table 1).

The proportion of women with bachelor/postgraduate education was substantially higher in both screened group and non-screened group with ANC visits (40.6% and 39.4%, respectively) compared to non-screened group without ANC visits (27.3%). At the same time, the highest percentage of women who had completed only primary school was observed in non-screened group without ANC visits (16.6%) (Table 1).

Table 1: Selected characteristics of the study sample by screening status in the Georgian Birth Registry, 2017/18 (n=103 079)

	Screened group	Non-screened group		p-value
		With ANC visits	Without ANC visit	
Women, N (%)	88 344 (85.7%)	8949 (8.7%)	5786 (5.6%)	
Age, mean (SD)	28.1 (5.7)	28.3 (5.8)	28.4 (6.2)	<0.001
Age group, N (%)				
≤24	25 739 (29.1%)	2603 (29.1%)	1710 (29.6%)	
25-34	49 508 (56.0%)	4914 (54.9%)	3023 (52.2%)	
≥35	13 097 (14.8%)	1432 (16.0%)	1053 (18.2%)	
Education, N (%)				<0.001
primary	6730 (8.3%)	1087 (13.9%)	749 (16.6%)	
secondary	41 469 (51.1%)	3652 (46.7%)	2529 (56.1%)	
bachelor, postgraduate	32 891 (40.6%)	3083 (39.4%)	1228 (27.3%)	
Region of ANC clinic, N (%)				<0.001
Guria	1416 (1.6%)	27 (0.3%)		
Adjara	10 127 (11.5%)	1360 (15.2%)		
Imereti	11 513 (13.0%)	614 (6.9%)		
Kakheti	4773 (5.4%)	764 (8.5%)		
Kvemo Kartli	7973 (9.0%)	686 (7.7%)		
Mtskheta-Mtianeti	412 (0.5%)	26 (0.3%)		
Racha-Lechkhumi, Kvemo Svaneti	151 (0.2%)	23 (0.3%)		
Smagrelo, Zemo Svaneti	5208 (5.9%)	438 (4.9%)		
Samtskhe-Javakheti	3079 (3.5%)	87 (1.0%)		
Shida Kartli	4934 (5.6%)	202 (2.3%)		
Tbilisi	38 758 (43.9%)	4722 (52.8%)		
Perinatal mortality, N (%)				<0.001
Yes	967 (1.1%)	106 (1.2%)	173 (3.0%)	
No	87 377 (98.9%)	8843 (98.8%)	5615 (97.0%)	
Complication during delivery, N (%)				<0.001
Yes	11 821 (13.4%)	835 (9.3%)	692 (12.0%)	
No	76 523 (86.6%)	8114 (90.7%)	5095 (88.0%)	
Birth weight, mean (SD)	3265.6 (558.1)	3250.6 (561.2)	3731.3 (668.2)	<0.001
Parity, N (%)				<0.001
0-1	34 436 (39.0%)	3317 (37.1%)	1797 (31.1%)	
2-4	48 550 (55.0%)	4909 (54.9%)	3089 (53.4%)	
4-15	5333 (6.0%)	711 (8.0%)	898 (15.5%)	

The results from multivariable binary logistic analysis showed an association between HCV screening attendance and mothers age at delivery; women older than 34 years of age had 9% lower odds of being screened compared to women in the age group 25-34 (95% CI 0.85-0.97), while the association was not observed in women younger than 25 year of age (OR=1.00, 95% CI 0.95-1.06) (Table 2).

Women who had completed only primary school had 49% lower odds of being screened, while those with bachelor and postgraduate education had 9% higher odds of being screened compared to women with secondary education (95% CI 0.47-0.55; 95% CI 1.03-1.15, respectively) (Table 2).

Table 2: Odds ratios (ORs) with 95% confidence intervals (CI) of screening status according to age, education, and region of ANC clinic in the Georgian Birth Registry, 2017-2018 (n=88 912)

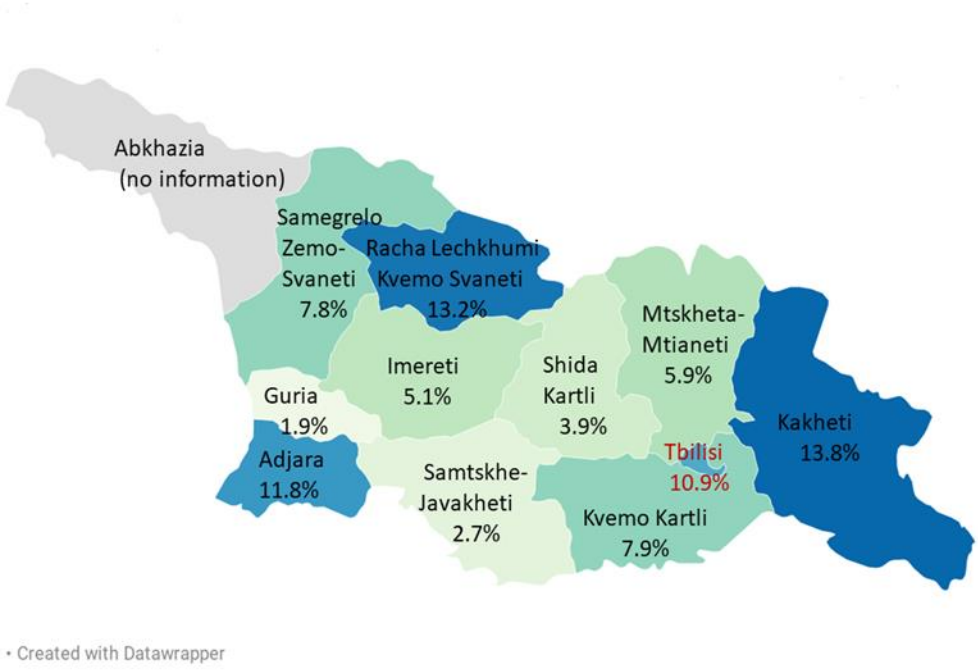
	Crude OR (95% CI)	**Multivariable adjusted OR (95% CI)**
Age		
≤24	0.98 (0.93-1.03)	1.00 (0.95-1.06)
25-34	1.00	1.00
≥35	0.91 (0.85-0.97)	***0.91 (0.85-0.97)***
Education		
Primary	0.55 (0.51-0.59)	***0.51 (0.47-0.55)***
Secondary	1.00	1.00
Bachelor, postgraduate	0.94 (0.89-0.99)	***1.09 (1.03-1.15)***
Region of ANC clinic		
Guria	1.00	1.00
Adjara	0.14 (0.10-0.21)	***0.14 (0.09-0.20)***
Imereti	0.36 (0.24-0.53)	***0.33 (0.22-0.49)***
Kakheti	0.12 (0.08-0.18)	***0.13 (0.09-0.19)***
Kvemo Kartli	0.22 (0.15-0.33)	***0.27 (0.19-0.41)***
Mtskheta-Mtianeti	0.30 (0.17-0.52)	***0.20 (0.17-0.52)***
Racha-Lechkhumi, Kvemo Svaneti	0.13 (0.07-0.22)	***0.13 (0.07-0.23)***
Samegrelo, Zemo Svaneti	0.23 (0.15-0.34)	***0.21 (0.14-0.32)***
Samtskhe-Javakheti	0.68 (0.44-1.04)	0.69 (0.44-1.07)
Shida Kartli	0.47 (0.31-0.70)	***0.44 (0.29-0.66)***
Tbilisi	0.16 (0.11-0.23)	***0.15 (0.10-0.22)***

Adjusted for: age, education, region of ANC clinics

3.3 Differences between regions and among ANC clinics in Tbilisi according to screening attendance

Kakheti region had the highest percentage of non-screened women (13.8%) followed by Racha-Lechkhumi with Kvemo Svaneti (13.2%), Adjara (11.8%), and Tbilisi regions (10.9%). The lowest proportion of non-screened women was reported in Guria region (1.9%) (Figure 2).

Figure 2. Percentage of unscreened women by regions in Georgia 2017/18



There were pronounced differences in screening attendance between ANC clinics in Tbilisi. In ten ANC clinics that were used in the analysis, the percentage of non-screened women ranged from 2.7% to 74.4% (Table 3).

Table 3: Percentage of screened and non-screened women at ten ANC clinics in Tbilisi selected by the highest number of non-screened women, 2017/18 (n=43 480)

	Screened group	Non-screened group
N (%)	38 758 (89.1%)	4 722 (10.9%)
ANC clinics, Tbilisi N (%)		
1.	171 (25.6%)	496 (74.4%)
2.	222 (52.4%)	202 (47.6%)
3.	1 324 (63.5%)	761 (36.5%)
4.	417 (80.0%)	104 (20.0%)
5.	579 (81.7%)	130 (18.3%)
6.	2 498 (87.6%)	354 (12.4%)
7.	2 039 (89.7%)	233 (10.3%)
8.	1 559 (91.0%)	154 (9.0%)
9.	1 949 (91.5%)	181 (8.5%)
10.	4 093 (97.3%)	113 (2.7%)
Remaining clinics	23 907 (92.3%)	1 994 (7.7%)

Further, the screening attendance was associated with the region of ANC clinic. Women with their first antenatal visit performed in Shida Kartli region had 56% lower odds to be screened for HCV during pregnancy, compared to Guria region (95% CI, 0.29-0.66). Odds of being screened in Imereti, Kvemo Kartli or Samagrelo with Zemo Svaneti regions, were 67%-79% lower compared to Guria region (OR=0.33, 95% CI 0.22-0.49; OR=0.27, 95% CI 0.19-0.41; OR=0.21, 95% CI 0.14-0.32, respectively). Finally, women who had their first antenatal visit in Kakheti, Racha-Lechkhumi with Kvemo Svaneti, Adjara, Tbilisi or Mtskheta-Mtianeti regions, had 80%-87% lower odds of being screened for HCV compared to women who had the first antenatal visit in Guria region (OR=0.13, 95% CI 0.09-0.19; OR=0.13, 95% CI 0.07-0.23; OR=0.14, 95% CI 0.09-0.20; OR=0.15, 95% CI 0.10-0.22; OR=0.20, 95% CI 0.17-0.52, respectively) (Table 2). Further adjustment for parity (number of deliveries including current delivery) did not change the estimates (results not shown).

3.4 Difference in perinatal mortality according to screening attendance

Non-screened women without ANC visits had a higher percentage of PM cases (3.0%) compared to screened women (1.1%), and non-screened women with ANC visits (1.2%) (Table 1).

There was no association between HCV screening attendance and PM in the multivariable binary regression analysis (OR=0.98, 95% CI 0.79-1.22) (Table 4). After including education, regions and parity into analysis there was no significant change in the estimate (OR=0.93, 95% CI 0.74-1.18). Sensitivity analysis which included only screened women and non-screened women without ANC visits showed a positive association between non-attendance to HCV screening and PM (OR=1.56, 95% CI 1.29-1.87).

Table 4: Odds ratios (ORs) with 95% confidence intervals (CI) of screening status according to perinatal mortality in the Georgian Birth Registry, 2017/18 (n=103 079)

	Crude OR (95% CI)	Multivariable adjusted OR (95% CI)
Perinatal mortality		
No	1.00	1.00
Yes	0.92 (0.76-1.13)	0.98 (0.79-1.22)

Adjusted for: age, birth weight, complications during delivery

4 Discussion

4.1 Discussion of the main results

The main findings of this thesis are that women who had only primary education completed had lower odds of being screened for HCV, and women with bachelor/postgraduate diploma had higher odds of being screened compared to women with secondary education level. Looking at the age groups, pregnant women who were 35 years of age or older had lower odds of being screened compared to women who were between 25-34 years old. Finally, considerable variation in attendance rate across the regions was observed.

Georgia is one of very few countries in the world that offers screening for HCV to all pregnant women. Universal screening for HCV, as opposed to risk-based screening which is adopted by most countries, is available in Ireland, Spain, Latvia, Australia, while in the US universal screening for HCV for all adults 18-79 years of age, including pregnant women, is recommended by the American Association for the Study of Liver Disease-Infectious Diseases Society of America 2019 guidelines (46-48). Hence, comparing the findings from Georgia presented in this study with findings from other countries is challenging, as to my knowledge there are no studies with similar aims conducted in countries with universal screening for HCV in pregnancy.

4.1.1 Differences in age and education between screening attendance groups

Data from the GBR show that women older than 35, and women with fewer years of attained education were less likely to be screened for HCV during pregnancy. An Australian report on

ANC attendance has shown that women older than 35 years of age, as well as those with fewer years of attained education and those with more previous births were found to have their first ANC visit later in their pregnancy and preferred fewer ANC visits (47). A late first ANC visit, resulting in the visit being outside of the period when screening for HCV is recommended (11^{th}-13^{th} week of pregnancy) could be a reason for a pregnant woman not being screened for HCV (49). Haddrill *et al*. have found several reasons why pregnant women had their first ANC visit late in pregnancy. They defined them as "late bookers" and the reasons lie in socio-cultural and psychological factors, as well as in empowerment. Lack of reproductive health knowledge, deferred recognition of pregnancy and previous experience with pregnancies may have led women to delay their first ANC visit. Women`s underestimation of the value of ANC and possible benefits for both mother and child could result in a late booking of first ANC visit or no visits at all (50), and consequently, with a possibility not to be screened for HCV.

During the study period, in Georgia, women over the age of 34 contributed the most to the total proportion of non-screened women. At the same time, 54.2% of them were with bachelor/postgraduate education.

Education was previously found to be a determinant when it comes to other types of screening in pregnancy. One study from Poland found that age, place of residence, and education are strong factors that influence screening attendance for HBV, HCV, Rubella, and *Toxoplasma gondii* at least once during pregnancy (51).

Higher education is associated with high SES and urban living, and with good experience in previous pregnancies (52). El-ghitany *et al.* have shown that highly educated women in Egypt, were more often screened for HCV before pregnancy, indicating that relevant

knowledge about hepatitis C was associated with educational level (53). Further, less educated and unemployed women could have less health education and knowledge about hepatitis C and importance of screenings during pregnancy (50). Moreover, there is a possibility that less educated women who have been screened in a previous pregnancy will not repeat screening again in a new pregnancy. However, after conducting a sensitivity analysis by including parity into multivariable logistic regression model, the estimates of the main predictors did not substantially change.

The quality of ANC has been evaluated in several countries with recommendations for improvement. In Kenya, low educated women and those in lower SES groups were less likely to be offered recommended screenings in pregnancy (49). Reasons for this could be a lack of good coordination with guidelines for screening in pregnancy as the result of medical professional's lack of knowledge (54).

Further, a study from US has shown that a number of low-income women rejected recommended screening during pregnancy. Women who regularly drink alcohol and/or use drugs have been shown to be less likely to undergo ANC or to attend a recommended number of visits, to report late for the first ANC examination, and to refuse offered screening during pregnancy for reasons not be related to alcohol or drug use (55). Information on alcohol and drug use among pregnant women in the GBR were incomplete and could not be used for analysis in this thesis. However, Georgia has one of the highest prevalence of injecting drug use in the world, and use of illicit drugs is very high, especially among youth. Kirtadze *et al.* reported results from a survey conducted in 2015 suggesting that 29.9% of Georgian residents have tried cannabis, while estimated prevalence of ever using heroin was 8% (56). A study from 2017, conducted by Mokhtari *et al.* found that 34.8% of Georgian pregnant women

drank alcohol in the past 30 days. Young pregnant women, those who were married, and those with the lowest income had the highest likelihood for alcohol use and binge drinking (57).

4.1.2 Geographical differences in screening attendance and possible influential factors

The economic development of the regions in Georgia does not explain fully the differences in the HCV screening attendance in pregnancy across the regions. According to data from 2016, poverty rates vary across regions in Georgia. The proportion of low-income households ranged from 11.8% in the Samata Javkheti region, 18.6% in Guria, to 39.5% in Mtskheta Mtianeti.

Kakheti and Adjara regions had 13.8% and 11.8% of non-screened women in this study, and had a similar proportion of low income residents recorded in 2016 - 25.8% and 26.8%, respectively (58). Mtskheta-Mtianeti and Samatskhe-Javakheti regions, which had highest and lowest percentage of poor residents in Georgia respectively, had both low percentage of non-screened women. On the other hand, Guria, the region with the lowest number of non-screened women had a higher percentage of low income residents than Samatskhe-Javakheti region (58). The people with low income live mainly in rural regions, are less educated, mostly do agriculture, have more members living in same household, and have more children (58). Miteniece *et al.* suggested that due to poor infrastructure, there are differences in access to ANC and offered screening in rural and mountainous areas compared to urban areas of Georgia (59).

Some consideration should also be given to the coverage of regions by the national screening for HCV, which targets population over 18 years of age. Data show that between 2015-2019, the percentage of screened adult population ranged from 38.7% in the Samatskhe-Javakheti region to 79.6% in the Racha-Lechkumi with Kvemo Svaneti region (18). In Guria, screening coverage was 77.2%, while just above half of the adult population in Kakheti region was screened for HCV. In regions with a high percentage of adult screening, it is possible that women who came for ANC, provided evidence of screening before pregnancy, and health personal used this data to record in the GBR that screening was done. This would be a possible explanation for Guria region in which only 1.9% of pregnant women were not screened for HCV in 2017/18. However, this assumption does not explain a high percentage of unscreened women recorded in Racha-Lechkhumi region (13.2%), which at the same time had 79.6% of the adult population screened.

In certain regions, as well as selected ANC clinics in Tbilisi, healthcare professionals might have recommended screening based on existing hepatitis C risks. The opportunity for a health care provider to make individual decision whether to recommend screening for hepatitis C during pregnancy, although recommended for all pregnant women, could be an indicator of insufficient transparency of the data, lack of compliance to existing protocols, and poor monitoring of the work of ANC clinics.

Other possible reason for the significant differences in screening attendance between the regions could be the differences in motivation and commitment of health personal who were responsible for feeding the data into the GBR to provide accurate and complete information (59).

4.1.3 Variations in screening attendance across antenatal clinics in Tbilisi

Pregnant women in Tblisi in 2017/18, represented 10.9% of pregnant women who had not been screened for HCV in Georgia. In the study period, a total of 263 ANC clinics conducted HCV screening for pregnant women, and differences were observed in screening attendance between the clinics. ANC clinics receive stimulation for the complete data entered for each woman who visited the clinic (43). Five ANC clinics stood out with a markedly high percentage of non-screened women of the total number of pregnant women registered at those clinics. Since all fields in the GBR need to be filled out, regardless of whether the screening is done or not, there is a possibility of false reporting. Data from ANC clinics were not synchronized with the medical records of pregnant women from their GPs, so there was no possibility of verification. Finally, there is a possibility that HCV screening was performed during one of the later visits rather than the first one. Even though the data from the GBR does not indicate that this was true, i.e. none of the women that were not screened during the first visit were registered as screened later during their pregnancies, there is a possibility that a person responsible for data entrance simply did not register in the GBR that a woman was subsequently screened. However, if true, this error is more likely to be random rather than systematic.

4.1.4 Perinatal mortality across screening attendance groups

To my knowledge, there is no previous evaluation of PM in relation to HCV screening attendance among pregnant women. The results presented here show that odds for being screened for HCV of mothers with perinatal loss, were similar to odds of mothers without. In

this analysis, women that were not screened comprised of those that had ANC visits and those who did not. However, the sensitivity analysis which compared screened women to those women who were not screened and did not attend any ANC visits showed that non-attendance to HCV screening was positively associated with PM. The null association that was observed in the overall analysis is most likely determined by if the woman had ANC visits or not. Manjavidze *et al.* has previously shown that the risk of PM is doubled in women in Georgia who did not have any ANC visits during pregnancy (36). Therefore, it is likely that the association observed in the sensitivity analyses is due to complex sociodemographic differences and not related to HCV screening. Manjavidze *et al.* have found that older pregnant women, women with only primary education and those who had lived outside of Tbilisi and gave birth in Tbilisi were more likely to have expirinced PM (36).

4.2 Strengths

The strength of this study is its sample size. This study included all women who gave birth in Georgia during 2017/18 that were recorded in nationwide data in GBR, and almost all were included in the analysis, making the results of this study representative for the pregnant women in Georgia. Another strength is high reliability of variables age, education, regions of ANC clinic, and PM.

4.3 Limitations

4.3.1 Selection bias

Selection bias occurs when cases and controls or exposed and unexposed participants are selected in the way that makes them not representative of the source population. This form of bias also occurs when study non-responders differ from those who do participate in the study (60, 61).

Even though registering the information in the GBR is mandatory, there were women without registered antenatal visit. If these women differed in any characteristic that is of interest from the women that were registered in the GBR, this could introduce a selection bias. Women who had unintended pregnancies, thus had no information on region of first ANC visit, were slightly older and lower educated compared to women with ANC visits.

A total of 8 381 women had a missing information for educational level. Out of those women 13.5% were non-screened for HCV, compared to 8.8% of women who had information on education in GBR. If majority of women who had missing information on education had only completed primary school, the true ORs for screening attendance between women with secondary and primary school would have been even larger.

4.3.2 Information bias

Information bias occurs as a consequence of a systematic error in measurement of exposure or/and outcome and results in misclassification of study participants (60). Misclassification of an exposure can be classified as either differential when the misclassification is independent

of the outcome, or non-differential when the proportion of those misclassified is different between participants relative to the study outcome (60).

The information from the GBR used in the thesis was not self-reported, thus the risk of misclassification should be small. Although the data in the GBR were entered by trained physicians and nurses during every antenatal visit, there is still a possibility of misclassification due to accidental mistypes. Additional limitation is that the information in the GBR was not validated against medical records (37). Finally, there was a possibility that woman had first ANC visit at one region, and additional visits at another, where screening for HCV could have been done. From the dataset used, there were no indications that this was true; the region of first visit corresponded to regions of subsequent ANC visits.

4.3.3 Confounding

A confounder is a factor that distorts a true association between exposure and outcome. In order for a factor to be a confounder, it has to be associated with both exposure and outcome while not being in the causal pathway between said exposure and outcome (61). Residual confounding occurs when the adjustment for confounding factors was performed inadequately, in the presence of additional confounders that were not taken into account, or due to a measurement error of confounding factors (62).

Binary logistic analysis used to quantify the association between PM and HCV screening attendance was adjusted for three selected factors (age, birth weight and complications during pregnancy), which, based on the literature, could affect the association between HCV screening attendance and PM. Even though the sensitivity analysis in which education, region

of first ANC visit, and parity were added in the multivariable model did not result in change of the estimate and hence indicate that the association was not strongly confounded by these factors, the possibility of residual confounding due to other factors or due to a measurement error cannot be excluded.

Smoking during pregnancy, alcohol consumption and drug use, as factors which are associated with birth weight, longevity of pregnancy and PM could have acted as unmeasured confounders in the logistic regression analyses. Information on these factors were unreliable and almost certainly underreported in the GBR (63). However, adjustment for birth weight might have partially taken into account smoking status in the analysis, as smoking is associated with low birth weight (64).

5 Conclusion

Data from the GBR from 2017 and 2018 showed that there were socio-demographic differences between pregnant women who have been screened for HCV and those who were not. Older pregnant women and those with only completed primary education were less likely to have been screened for HCV during pregnancy. There were substantial differences in screening attendance rates between regions in Georgia. Guria was the region with lowest proportion of non-screened women. Similarly, there were noticeable differences in screening attendance rates between ANC clinics in Tbilisi. There was no association between HCV screening attendance and PM.

6 Implication for screening practices

The results from this thesis could have important implications for recommended screening for HCV in pregnancy in Georgia. Furthermore, as it is difficult to separate screening for HCV from other recommended services included in ANC the implications could be expanded to quality of ANC in general and adherence to ANC guidelines.

Improvement of prenatal care, education programs about reproductive health, and increased awareness of importance of ANC visits and recommended screenings, including screening for HCV, would improve HCV screening attendance. Family planning programs for women in reproductive age should provide concise information about HCV transmission and importance of offered screenings during every pregnancy. Results of this thesis underlie the importance of improving quality of ANC in rural parts of the country, among older and less educated pregnant women.

Special attention should be given in providing better local control of health facilities which provide antenatal care as well as control by the government. Improved control of health providers work by matching ANC files with general medical files should lead to better reporting of information to the GBR. Planning and conducting continued medical education for health providers who work in the field of ANC, with special attention on improving how the data are entered into the GBR, as well as on improving the recruitment approach of pregnant women depending on their age and level of education, could lead to more reliable data in the GBR and improved HCV screening attendance.

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